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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,298	05/20/1999	CHING-LEOU TENG	ISIS-3510	6350

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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,298	TENG ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,13,19,20,80,84,85,91 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,13,19,20,80,84,85,91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-24-04 has been entered.

Response to Arguments

2. In the response filed 3-24-04 Applicants stated that during the interview of 2-04-04, the examiner indicated that claim 1 would be looked upon favorably if it were amended to recite specific bile salts (as set forth in original claim 12). However, it is also noted that the Examiner stated that the favorable consideration of Applicant's amendment would be contingent upon an updated search. An updated search was performed, which identified new prior art, a new grounds for rejection is set forth below.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application

being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1, 91, 95 are rejected under 35 U.S.C. 102(e) as being anticipated by New et al. (WO 98/00169 A1; International Publication Date 1-08-98).

The instant claims are drawn to a composition comprising at least one oligonucleotide in an emulsion and a bile salt, wherein said bile salt is selected from the group consisting of cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether and a pharmaceutically acceptable salt thereof.

New et al. disclose hydrophobic preparations comprising: an oil phase comprising one or more medium chain monoglycerides; at least one amphiphile; and a hydrophilic species solubilised or otherwise dispersed in the mixture of glycerides; wherein the hydrophilic species is one that is not normally soluble in the one or more monoglycerides (page 2, lines 7-18). The hydrophobic preparations of the New et al. invention are extremely versatile and have many applications. They may either used alone or they may be combined with an aqueous phase to form an emulsion or similar two-phase composition that forms a second aspect of the invention (see page 9, lines 12-15). In one preferred embodiment the amphiphile is a bile salt (page 4, lines 6-9), the bile salt may be either unconjugated or conjugated, examples of unconjugated bile salts include: cholate, ursodeoxycholate, chenodeoxycholate, and deoxycholate (page 4, lines 26-29). Examples of conjugated bile salts include taurocholate, glycocholate,

taurodeoxycholate and glycodeoxycholate (page 5, lines 1-5). The "hydrophilic species" of the present invention relates to any species that is generally soluble in aqueous solvents but insoluble in hydrophobic solvents. Examples of hydrophilic molecules that included in the present invention include proteins, glycoproteins, oligo and polynucleic acids, for example DNA, e.g. plasmid DNA, and RNA, as well as DNA and/or RNA analogues (page 5, lines 14-24).

In another aspect of the New et al. invention, the hydrophobic preparations can be used in the preparation of a medicament for oral delivery or a hydrophilic species (page 10, lines 1-8), or may also provide for other routes of administration, e.g. topical or vaginal (page 10, line 1).

The emulsions of New et al. comprising a hydrophobic preparation comprising a bile salt as an amphiphile, and an "oligo" as a hydrophilic species, as described above, anticipates the instant invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4-7, 13, 19-20, 84-85, 91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. in view of New et al. (WO 98/00169 A1), and Nielsen et al.

Kawai et al. disclose lipid microsphere in fat emulsion as a carrier to transducing gene DNA (i.e., microemulsion). These compositions comprise at least a transducing

gene DNA, wherein said transducing gene DNA is synthetic oligonucleotide, such as the so-called phosphorothioate type, or it is a structural gene integrated into a vector (page 13, last paragraph of Japanese translation). Moreover, the compositions of the Kawai et al. invention comprise a transducing-gene DNA; fat emulsion base of at least one kind chosen from a vegetable oil, triglyceride of the medium chain triglyceride of 8-12 carbon atoms (such as capric, lauric and caprylic acid, see page 16, paragraph [0013]), fatty acids of 6-18 carbon atoms (penetration enhancer); the emulsifier of at least one kind chosen from a phospholipid and a nonionic surface active agent; a cholesterol derivative; and water (see summary of the invention, page 3 of the Japanese translation). It is assumed from the reference that the emulsions are oil-in water emulsions since they are described in the Japenese translation as being fat emulsions wherein the water serves as the solvent (page 18, paragraph [0016] of translation).

The "transducing-gene DNA" of Kawai et al. is chosen from cancer suppression gene DNA, gene DNA of an interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-7, GM-CSF, TNF-alpha, interferon-c, PDGF (cell adhesion protein), HVS-tk, diptheria-toxin A, and cytosine deaminases (see 3rd paragraph of page 5, Japanese translation).

In another embodiment of Kawai et al., an emulsifier is distributed above the fat emulsion, wherein the emulsifier is a phospholipid or a nonionic surface-active agent (page 17, paragraph [0015]).

Moreover, the fat emulsions of Kawai et al. can be made to contain further additive agents, such as an isotonizing agent emulsification support agent, a stabilizer (for

example, wherein said stabilizer is dextran see page 20, paragraph [0020]), and a pH manufacture agent (page 18, paragraph [0017]).

However, Kawai et al. does not disclose emulsions comprising a bile salt, wherein said bile salt is selected from the group consisting of: cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether. Neither does Kawai et al. disclose compositions comprising an oligonucleotide wherein said oligonucleotide is selected from the group consisting of SEQ ID NO: 2, 48-50, 16, 19, and 51-54.

New et al. disclose hydrophobic preparations comprising: an oil phase comprising one or more medium chain monoglycerides; at least one amphiphile; and a hydrophilic species solubilised or otherwise dispersed in the mixture of glycerides; wherein the hydrophilic species is one that is not normally soluble in the one or more monoglycerides (page 2, lines 7-18). The hydrophobic preparations of the New et al. invention are extremely versatile and have many applications. They may either used alone or they may be combined with an aqueous phase to form an emulsion or similar two-phase composition that forms a second aspect of the invention (see page 9, lines 12-15). In one preferred embodiment the amphiphile is a bile salt (page 4, lines 6-9), the bile salt may be either unconjugated or conjugated, examples of unconjugated bile salts include: cholate, ursodeoxycholate, chenodeoxycholate, and deoxycholate (page 4, lines 26-29). Examples of conjugated bile salts include taurocholate, glycocholate, taurodeoxycholate and glycodeoxycholate (page 5, lines 1-5). The "hydrophilic species"

of the present invention relates to any species that is generally soluble in aqueous solvents but insoluble in hydrophobic solvents. Examples of hydrophilic molecules that included in the present invention include proteins, glycoproteins, oligo and polynucleic acids, for example DNA, e.g. plasmid DNA, and RNA, as well as DNA and/or RNA analogues (page 5, lines 14-24).

In another aspect of the New et al. invention, the hydrophobic preparations can be used in the preparation of a medicament for oral delivery or a hydrophilic species (page 10, lines 1-8), or may also provide for other routes of administration, e.g. topical or vaginal (page 10, line 1).

Nielsen et al. discloses pharmaceutical compositions that are intended for application to or through the mucosa of an animal, wherein the mucosa is preferably selected from oral, nasal, vaginal, rectal, aural, lung, and gastrointestinal mucosa (page 3, lines 4-8) . In one embodiment of the Nielsen et al. invention, the pharmaceutical composition comprises a biologically active substance, wherein said substance is ISIS-2922 (page 14, lines 19-22), which is an anti-herpes virus agent that is a phosphorothioate modified antisense oligonucleotide according to SEQ ID NO: 48 of the instant application (see also the Registry report of the sequence of ISIS-2922).

The compositions of Nielsen et al. that are specifically for oral administration may comprise pharmaceutically acceptable carriers or excipients, which may include (*inter alia*) penetration enhancers, ointment bases, excipients, emulsifying agents (i.e. forming an emulsion), and chelating agents (page 22, lines 5-12). The compositions or formulations of Nielsen et al. may also comprise emulsions, see page 21, lines 4-8, The

ointment bases of Nielsen et al. include fatty acids such as vegetable oils, and palmitate (page 23, lines 9-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kawai et al., New et al. and Nielsen et al. to make the claimed invention. Absent any evidence of unexpected results associated with the claimed compounds, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the compositions of Kawai et al. to further comprise bile salts, or to comprise the oligonucleotides disclosed in Nielsen et al. One of ordinary skill in the art would have been motivated to make this modification since the compositions of Kawai et al. are intended to provide carriers suitable for transducing gene DNA associated with cancer suppression genes, and DNA relevant to viral illness, and the antisense oligonucleotides of Bennett et al. and Nielsen et al. are disclosed as being useful for inhibiting the expression of genes associated with viral infection (see abstract of Nielsen et al.), respectively. Moreover, one of ordinary skill in the art would have been motivated to modify the compositions of Kawai et al. with the bile salts of New et al. for the expressed benefits of the presence of bile salts in pharmaceutical compositions according to New et al., specifically wherein the bile salts function to improve absorption of biologically active materials into cells.

Therefore, the invention as a whole would have been *prima facie* obvious over Kawai et al. in view of New et al. and Nielsen et al.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 80 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

Claim 80 was amended to recite "[T]he composition according to claim 1, wherein said oligonucleotide comprises ~~is~~ SEQ ID NO: 1." However, Applicants have not provided any explanation of why this amendment was necessary or where support for this amendment can be found in the specification as filed. As per MPEP § 608.04 no amendment may introduce new matter into the disclosure of an application after its filing date. Applicants must cancel the new matter in response to this Office Action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE